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Synthesis of 7-Methyl-2-Oxo -2,4,5,6-Tetrahydropyrrolo[1,2-c] Pyrimidine

by
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November 1964

EDGEWOOD ARSENAL, MARYLAND 21010

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SYNTHESIS OF 7-METHYL-2-OXO-2,4,5,6-TETRAHYDROPYRROLO[1,2-c]PYRIMIDINE

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FOREWORD

The work described in this report was performed in conjunction with contract DA-18-108-Cml-5998 and Task 1C522301A06007, Research on Natural Products (U). The experimental data are recorded in unclassified notebooks I and II. The work was started in September 1960 and was completed in June 1961.

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DIGEST

As part of a study for the elucidation of the structure of saxitoxin, the synthesis was undertaken of a possible C_8 fragment resulting from the degradation of the natural product.

The preparation of 7-methyl-2-oxo-2,4,5,6-tetrahydropyrrolo[1,2-c]-pyrimidine, a new ring system, is described.

It was concluded that:

1. The selective oxidation to the desired 7-methyl-2-oxo-2,4,5,6-tetrahydropyrrolo-[1,2-c]pyrimidine was accomplished with a dilute neutral aqueous solution of potassium permanganate at room temperature overnight.

2. The physical and analytical properties of 7-methyl-2-oxo-2,4,5,6-tetrahydropyrrolo-[1,2-c]pyrimidine were not identical with those of the product obtained from the natural product.

3. The 8-methyl derivative is the correct structure of one of the degradation products of saxitoxin.

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SYNTHESIS OF 7-METHYL-2-OXO-2,4,5,6-TETRAHYDROPYRROLO[1,2-c]PYRIMIDINE

I. INTRODUCTION.

The nonhydrolytic degradation of clam poison with phosphorus and hydriodic acid in acetic acid yields a fragment having the empirical formula $C_8H_{10}N_2O$.* On the basis of the ultraviolet and infrared spectra, this fragment was postulated to contain a pyrrolo[1,2-c]pyrimidine bicyclic ring system, a new ring system accounting for seven of the carbon atoms. Preliminary studies by nuclear-magnetic-resonance (NMR) spectroscopy demonstrated that the remaining methyl group, which completes the C_8 system, is located in the 6-, 7-, or 8- position of the pyrimidine ring.

This study was undertaken to prepare the 7-methyl derivative for comparison with the C_8 fragment obtained from the natural product.

II. EXPERIMENTATION.

A. Preparation of Methyl 2-Bromopropionate.

A 95.0-gm (0.444 mole) sample of α-bromopropionyl bromide was placed in a 300-ml round-bottomed flask equipped with a magnetic stirrer. A slow stream of dry nitrogen was passed through the apparatus to blanket the reaction mixture while the flask was cooled to -15°C. Methanol (45 ml, 1.15 moles) was then added slowly from a dropping funnel. After the addition was completed, the solution was stirred for 1 hr at -15°C and for 0.5 hr at +15°C. The mixture was then diluted with 250 ml of ether. After the organic layer was washed with 250 ml of water and 250 ml of 10% sodium bicarbonate, the ether phase was dried over anhydrous potassium carbonate. Vacuum distillation yielded 62.5 gm (84.8%) of methyl 2-bromopropionate, bp 68° to 70°C/27.0 mm.

B. Blaise Reaction of Methyl 2-Bromopropionate With Methyl 3-Cyanopropionate.

A mixture of 26.0 gm (0.23 mole) of methyl 3-cyanopropionate, 20.0 gm (0.306 mole) of freshly sandpapered zinc foil, 250 ml of sodium-dried benzene, and 100 mg of mercuric chloride was placed in a 1-ℓ, triple-necked, round-bottomed flask with a Hershberg stirrer, dropping funnel, and

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* Rapoport, H., and Schuett, Wolfgang. J. Am. Chem. Soc. 84, 2266-2267 (1962).

condenser; a stream of nitrogen was passed through the apparatus to blanket the reaction mixture. A solution of 35.0 gm (0.21 mole) of methyl 2-bromopropionate in 250 ml of sodium-dried benzene was added from the dropping funnel to the warm reaction flask with rapid stirring. After approximately one-half of the solution had been added, the reaction mixture gradually became turbid and yellow. The mixture was then refluxed for 2 hr, at which time a red gum formed. The reaction mixture was cooled, and 300 ml of 15% sulfuric acid (47.2 ml of concentrated sulfuric acid in 250 ml of water) was added and stirred for 1 hr at room temperature. The layers were separated, the aqueous layer was extracted with two 250-ml portions of benzene, and the combined benzene layers were washed with five 50-ml portions of water. After this solution was dried overnight over anhydrous potassium carbonate, the solvent was removed with a rotary evaporator, and the residue was distilled in vacuo. After an 8.01-gm fraction of recovered 3-cyanopropionate was removed, a fraction was collected at 110° to 133°C/4.0 mm (solidified), which was crystallized from water and sublimed to give 12.4 gm (46.6% based on cyano ester used) of 5-(1-methoxycarbonyl-1-ethylidene)-2-pyrrolidinone (I), mp 87.8° to 88.5°C.

Analysis of $C_8H_{11}NO_3$:

Calculated: C, 56.79; H, 6.55; N, 8.28; OCH_3, 18.37
Found: C, 56.58; H, 6.49; N, 8.14; OCH_3, 18.71

Ultraviolet data - λ_{max} 267 mμ (ε 20,310)

Infrared data - 2.95μ, 3.40μ, 5.78μ, 5.94μ, 6.14μ

NMR data -

τ values	Proton resonance
8.26	$CH_3-C=$
7.60	$CH_2-C=$
7.31	$CH_2-\overset{O}{\overset{\|}{C}}-N$
6.41	CH_3-O
0.35	$N-H$

C. Catalytic Reduction of 5-(1-Methoxycarbonyl-1-ethylidene)-2-pyrrolidinone (I).

A mixture of 20.0 gm (0.118 mole) of (I) in 150 ml of glacial acetic acid, 1 ml of 70% perchloric acid, and 1.0 gm of platinum oxide was placed on a Parr low-pressure hydrogenator under 40 lb of hydrogen pressure at room temperature with rocking. The following pressure drops were noted.

Time	Pressure, lb	Percent of theoretical
12:00	40.0	0.0
12:05	37.9	21.8
12:15	37.0	30.9
12:30	36.2	39.2
1:00	35.6	45.4
5:00	32.8	74.3
8:00	30.0	100.3

The mixture was filtered and the solvent removed on the rotary evaporator. The residue was dissolved in 100 ml of 10% aqueous sodium bicarbonate and continuously extracted overnight with benzene. The benzene was evaporated, and the residue was crystallized from ethyl ether to yield 18.5 gm (91.5%) of 5-(1-methoxycarbonyl-1-ethyl)-2-pyrrolidinone (II), mp 90° to 92°C.

Analysis of $C_8H_{13}NO_3$:

Calculated: C, 56.12; H, 7.65; N, 8.18
Found: C, 55.80; H, 7.56; N, 7.89

Ultraviolet data - no absorption

Infrared data - 2.90μ, 3.40μ, 5.80μ, 5.95μ

D. Preparation of 2-(1-Carbamoyl-1-ethyl)-2-pyrrolidinone (III).

A solution of 4.5 gm (0.0262 mole) of (II) and 20 ml of 7.6 M methanolic ammonia was placed in a sealed glass tube and heated for 48 hr at 100°C. The tube was cooled and then opened, and the excess solvent and ammonia were removed on a rotary evaporator. The crude residue was crystallized from chloroform-carbon tetrachloride and dried in a vacuum for 48 hr at 90°C to yield 2.66 gm (64.7%) of (III), mp 155° to 156°C.

Analysis of $C_7H_{12}N_2O_2$:

Calculated: C, 53.83; H, 7.74; N, 17.94
Found: C, 53.95; H, 7.75; N, 18.13

Ultraviolet data - no absorption

Infrared data - 2.93μ, 3.40μ, 5.94μ, 6.24μ

E. Preparation of 2-(1-Amino-2-propyl)pyrrolidine (IV).

A suspension of 2.28 gm (0.06 mole) of lithium aluminum hydride in 32.2 ml of dry tetrahydrofuran (freshly distilled from P_2O_5) was prepared in a 250-ml round-bottomed flask equipped with a Hershberg stirrer, condenser, and drying tube; a steady flow of nitrogen was passed through to blanket the reaction mixture.

A slurry of (III) was added slowly at room temperature. After the mixture was refluxed for 6 hr and then cooled, 10 gm of ice water was added carefully. The pH was adjusted to 4 with 1 N hydrochloric acid and the solvent removed on a rotary evaporator. The residue was made strongly alkaline with 10 N potassium hydroxide and extracted with three 100-ml portions of chloroform. The combined organic layers were dried over anhydrous potassium carbonate and the solvent was stripped. The residue was distilled in vacuo to yield 1.4 gm (63.5%) of (IV), bp 66° to 66.5°C/1.0 mm.

Analysis of $C_7H_{16}N_2$:

Calculated: C, 65.57; H, 12.58; N, 31.85
Found: C, 65.60; H, 12.91; N, 31.59

Ultraviolet data - no absorption

Infrared data - 2.9μ to 3.3μ, 3.45μ, 3.95μ, 6.26μ

F. Preparation of 7-Methyl-2-oxo-1,2,4,5,6,6a,7,8-octahydropyrrolo[1,2-c]pyrimidine (V).

A solution of 1.4 gm (0.011 mole) of (IV) and 15 ml (0.12 mole) of diethyl carbonate was heated in a sealed glass tube for 9 hr at 200°C in an oil bath. The contents were cooled and placed on a rotary evaporator, and the excess diethyl carbonate was removed in vacuo. The residue was adsorbed on a 25-ml column of Dowex 50W-X8 ion-exchange resin (hydrogen form) with the aid of 50 ml of water. The column was washed with 300 ml of water and then eluted with 0.1 N ammonium hydroxide in 50-ml portions. The first three

alkaline fractions were evaporated to give 0.54 gm (32.0%) of (V), mp 160° to 163°C, after crystallization from chloroform and petroleum ether and after undergoing sublimation.

Analysis of $C_8H_{14}N_2O$:

Calculated: C, 62.30; H, 9.15; N, 18.17
Found: C, 62.57; H, 9.15; N, 17.86

Ultraviolet data - no absorption

Infrared data - 2.95μ, 3.45μ, 4.10μ to 4.20μ, 6.11μ, 6.24μ, 6.84μ

G. 7-Methyl-2-oxo-2,4,5,6-tetrahydropyrrolo[1,2-c]pyrimidine (VI).

To 1.36 gm (8.84 moles) of (V) in 1,360 ml of water was added 1,400 ml of an 0.2% solution of potassium permanganate (1.5 oxo. equivalents) at room temperature. The dark solution was left standing for 15 hr and then adsorbed on 120 ml of Dowex 50W-X8 (hydrogen form). The column was washed with 1 *l* of water and eluted with 250-ml portions of 0.1 N ammonium hydroxide. The first five alkaline fractions were evaporated, sublimed twice, and dried in a vacuum desiccator over magnesium perchlorate to yield 0.333 gm (25.3%) of (VI), mp 127° to 129°C.

Analysis of $C_8H_{10}N_2O$:

Calculated: C, 63.98; H, 6.71; N, 18.65
Found: C, 64.06; H, 6.71; N, 18.84

Ultraviolet data - λ_{max} 315 mμ (ε 6,400), 219 mμ (ε 13,400)

Infrared data - 2.92μ, 3.42μ, 4.14μ, 6.06μ (s), 6.18μ (s), 6.33μ, 6.43μ to 6.6μ (w), 6.73μ, 7.08μ, 7.28μ, 7.55μ, 7.80μ to 8.55μ

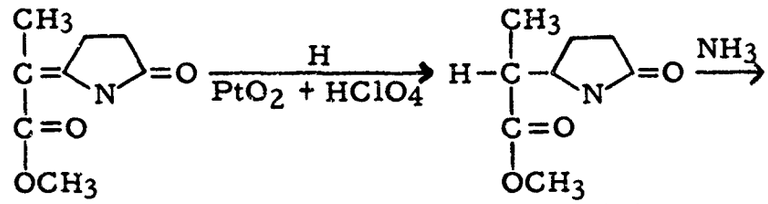
NMR data -

τ values	Proton resonance
1.77	N=CH
5.87	N−CH_2
6.90	=C−CH_2
7.93	−CH_2−

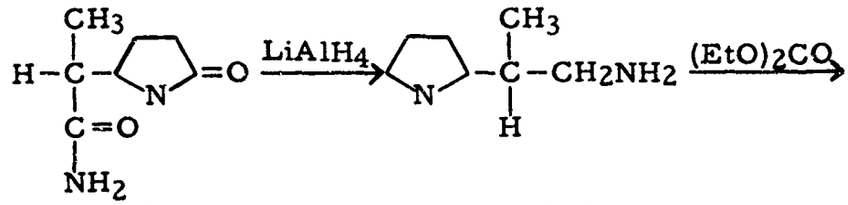
III. DISCUSSION OF EXPERIMENTAL RESULTS.

After trying several different unsuccessful ways of alkylating a properly substituted aliphatic side chain in the α-position of pyrrole for further cyclization, the method of Lapin and Horeau* for the preparation of α,α'-disubstituted pyrroles, dihydropyrrolenones, and dihydropyridones from aliphatic starting materials was utilized. The method involves a Blaise condensation of an α-bromo ester, a nitrile, and zinc to form a heterocyclic ring system containing nitrogen, as outlined in the following scheme.

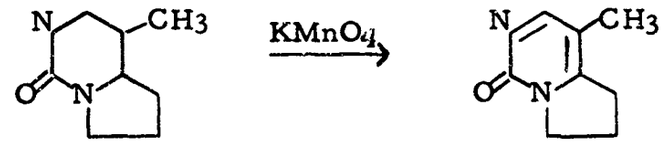
$$CNCH_2CH_2CO_2CH_3 + CH_3CHBrCO_2CH_3 + Zn \xrightarrow[HgCl_2]{}$$



(I) (II)



(III) (IV)



(V) (VI)

* Lapin, Henri, and Horeau, Alain. Bull. soc. chim. France 1960, 1703-1707 (1960).

The treatment of methyl 3-cyanopropionate and zinc foil with methyl 2-bromopropionate in dry benzene in the presence of a catalytic amount of mercuric chloride gave 46.6% of (I). The purification procedure was modified from that reported* for the tertiary butyl ester by distilling the crude reaction product in vacuo, since the attempted crystallization of crude product after removal of excess cyano ester resulted only in an impure product. The ultraviolet, infrared, and NMR spectra corroborated the presence of an exo-cyclic double bond.

The catalytic reduction over platinum oxide of this double bond under the conditions reported* for the tertiary butyl ester was surprisingly slow. After a catalytic amount of perchloric acid had been added, however, the hydrogen uptake proceeded at a very fast rate to form (II).

The ester function of (II) was converted to the amide group with methanolic ammonia under pressure at 100°C after other attempts at lower temperatures and longer periods of time gave only unreacted starting materials. The reaction was followed by the disappearance of the ester carbonyl absorption in the infrared spectrum at 5.8μ.

The reduction of (III), a diamide, with lithium aluminum hydride in refluxing tetrahydrofuran was completed after 6 hr. The colloidal precipitate obtained under strong alkaline conditions was extracted with difficulty with chloroform, which may explain the production of lower yields than was anticipated. Using a larger excess of lithium aluminum hydride did not improve the yield of the diamine (IV).

The cyclization was made with an excess of diethyl carbonate at 200°C in a sealed glass tube to form (V). The poor yield may be a result of noncyclic polymerization of the urea type (-N-C(=O)-N-).

The selective oxidation to the desired (VI) was accomplished with a dilute neutral aqueous solution of potassium permanganate at room temperature overnight.

The physical and analytical properties of (VI) were not identical with those of the product obtained from the natural product.

The 8-methyl derivative is the correct structure of one of the degradation products of saxitoxin.**

* Lapin, Henri, and Horeau, Alain. Bull. soc. chim. France 1960, 1703-1707 (1960).

** Rapoport, H., and Schuett, Wolfgang. J. Am. Chem. Soc. 84, 2266-2267 (1962).

IV. CONCLUSIONS.

It was concluded that:

1. The selective oxidation to the desired 7-methyl-2-oxo-2,4,5,6-tetrahydropyrrolo-[1,2-c]pyrimidine was accomplished with a dilute neutral aqueous solution of potassium permanganate at room temperature overnight.

2. The physical and analytical properties of 7-methyl-2-oxo-2,4,5,6-tetrahydropyrrolo-[1,2-c]pyrimidine were not identical with those of the product obtained from the natural product.

3. The 8-methyl derivative is the correct structure of one of the degradation products of saxitoxin.

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13 ABSTRACT

(U) This report describes a five-step, saxitoxin-degradation-product synthesis to obtain the 7-methyl derivative for comparison with the C_8 fragment from clam poison. Ultraviolet and infrared spectral analyses show that this fragment contains a pyrrolo[1,2-c]pyrimidine ring system, a new system accounting for seven of the carbon atoms. Nuclear-magnetic-resonance spectroscopy shows that the last methyl group completing the C_8 system lies in the 6, 7, or 8 position of the pyrimidine ring. The method consists of a Blaise condensation of an α-bromo ester and a nitrile with zinc to form a heterocyclic ring system containing nitrogen.

14. KEYWORDS

Spectra	Infrared	Aliphatic compounds
Esters	Saxitoxin	Physical properties
Fragments	Synthesis	Degradation process
Ultraviolet	In vacuo	Nuclear magnetic resonance
Clam poison	Spectroscopy	
Pyro compounds	Bicyclic compounds	

Pyrimidine, 7-methyl-2-oxo-2,4,5,6-tetrahydropyrrolo[1,2-c]

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